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Research paper

Cannabis use, depression and anxiety: A 3-year prospective population-based study

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ABSTRACT

Background: Whether or not cannabis use may increase the risk for depression and/or anxiety is not clear. For one thing, it has not been possible to draw a definitive conclusion regarding the direction of causality, i.e. whether cannabis use increases the risk for depression/anxiety or vice versa. This study aimed at examining possible associations between cannabis use, depression and anxiety, using all three measures as both exposure and outcome.
Methods: Data were obtained from a longitudinal cohort study comprising 8598 Swedish men and women, aged 20–64, with a three-year-follow-up.
Results: Adjusted for sex and age, cannabis use at baseline was associated with an increased relative risk (RR) for depression and anxiety at follow-up, with RR=1.22 [1.06–1.42 CI 95%] for depression and RR=1.38 [1.26–1.50 CI 95%] for anxiety. Adjusted for all confounders (alcohol and illicit drug use, education, family tension, place of upbringing), the associations were no longer statistically significant; RR=0.99 [0.82–1.17 CI 95%] for depression and RR=1.09 [0.98–1.20 CI 95%] for anxiety. Age-adjusted, reporting depression or anxiety at baseline increased the risk of cannabis onset at follow-up three years later; RR=1.62 [1.28–2.03 CI 95%] and RR=1.63 [1.28–2.08 CI 95%] respectively. However, adjusted for other illicit drug use the associations were no longer statistically significant.
Limitations: Lack of information on frequency of cannabis use and of age of initiation of use.
Conclusions: We found no longitudinal associations between cannabis use and incidence of depression/anxiety, or between depression/anxiety and later cannabis use onset.

1. Introduction

Whether cannabis use increases the risk of depression has not been established. It has been suggested that the active ingredient in cannabis, tetrahydrocannabinol (THC), in the long term may affect serotonin and other neurotransmitters in ways that produces depressive symptoms (Martin et al., 2002). There is, however, little research evidence to support this direct effect of cannabis. Other possible suggested pathways are that cannabis use contributes to certain negative life events, for example disengagement from education, with an increased risk of unemployment and subsequent depression as a result (Lev-Ran et al., 2014; Degenhardt et al., 2003; Marmorstein and Iacono, 2011), or that the observed associations are instead results of overlapping risk factors, for example parental psychiatric disorders (Degenhardt et al., 2003) which increase the risk for both cannabis use and depression.

Results based on a Swedish male cohort showed an increased risk of hospitalization from depression in men reporting heavy cannabis use in adolescence, but this association disappeared after adjusting for conduct problems in childhood (Manrique-Garcia et al., 2012). A recent meta-analysis, pooling data from 14 studies, showed that cannabis use at early ages, particularly heavy use, was associated with an increased risk of depression (Lev-Ran et al., 2014). However, there was large heterogeneity in the included studies and, as stressed by the authors, further longitudinal studies are needed.

Another debated issue is whether cannabis use increases the risk of anxiety. About 20–30 percent show anxiety reactions after smoking cannabis as an immediate intoxication effect (Thomas, 1993), but whether cannabis is associated with anxiety also in a long term perspective is not clear. One longitudinal study found that adolescent cannabis use was associated with anxiety in young

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adulthood also after adjusting for a number of related factors, such as other substance use, education and family situation (Degenhardt et al., 2012). Other studies have also reported on this association (Moore et al., 2007; Crippa et al., 2009; Hayatbakhsh et al., 2007; Van Laar et al., 2007; Windle and Weisner, 2004), but the results are inconsistent since in many of these studies the associations have disappeared after covariate adjustments.

Thus, much of the relationship between cannabis use, depression and anxiety remains unclear. For one thing, it has not been possible to draw a definitive conclusion regarding the direction of causality. Many previous cohort studies have failed to control for baseline depression and/or anxiety (Lev-Ran et al., 2014; Crippa et al., 2009). Also, even though sex is known to affect both prevalence of depression and anxiety (Bahrami and Yousefi, 2011) as well as prevalence of cannabis use (Lev-Ran et al., 2014), with the former being higher in women and the latter higher in men; those discrepancies between the sexes have not been examined in more detail. A recent cross-sectional study showed cannabis use to be a better indicator of poor mental health in women than in men (van Gastel et al., 2014) and cannabis use disorder has been associated with major depressive disorders in females but not in males (Durdle et al., 2008). Still, possible longitudinal associations need further examination.

By using a population based cohort with data on cannabis use, depression and anxiety both at baseline and follow-up, we aimed to find out whether there is an association between cannabis use and depression and/or anxiety; the direction of the association and if the associations are different for men and women.

2. Methods

2.1. Study population

The analyses comprised data from the Mental Health, Work and Relations study (PART by Swedish acronym), a longitudinal population-based study on mental illness in Stockholm, Sweden. Five random samples of equal size were drawn from the Stockholm County population register ($N \approx 858.000$) at regular intervals between 1998 and 2000 (T_0) among Swedish citizens age 20–64 residing in Stockholm. In total, 19.742 individuals were sent a questionnaire, to which 10.441 responded (53%). These individuals were contacted again after three years with a postal questionnaire (2001–2003) (T_1), to which 8.613 responded (83%).

Non-participation was high, and has been analysed by comparing information from national registers for participants and non-participants in two previous studies, showing that those with low income, low education, of non-Nordic origin, unmarried and having a psychiatric diagnosis were less likely to participate (Lundberg et al., 2005; Bergman et al., 2010). Because questionnaire respondents who did not answer all questions were contacted by telephone and asked to give supplementary information, the internal missing (respondents' non-response to individual items) is generally low and this is also the case for the questions on drug use. At both waves of data collection (T_o and T_1), double-phase random subsamples were invited for psychiatric interview (Schedules for Clinical Assessment in Neuropsychiatry) in order to validate the psychiatric scales in the questionnaire (Forsell, 2005; Lundin et al., 2015a, 2015b).

The ethical review board at the Karolinska Institutet, Stockholm, approved the study, and informed consent was obtained from all participants.

3. Measures

3.1. Cannabis use

The study exposure was life-time cannabis use (T_0). Those who responded positive to a question on lifetime use of illicit drugs ("*Have you ever used narcotics?*") were asked to indicate which type(s) of drug(s) they had used. Six fixed alternatives were indicated: cannabis (hashish or marijuana), stimulants (e.g. amphetamine), opiates (opium, heroin, morphine, crack etc.), hallucinogens (e.g. LSD), cocaine and ecstasy. A second question asked about recency ("*When did you last use narcotics?*"), with six answer alternatives: today, last week, last month, last 12 months and more than 12 months ago. These two questions were converted into assumed cannabis consumption (a dichotomous variable, indicating ever use of cannabis). When examining possible reverse associations; cannabis use onset ("last 12 months or more often" at T_1) was instead the study outcome.

3.2. Depression and anxiety

Depression was measured using the *Major Depression Inventory* (MDI), both at T_0 and T_1 which asks about presence of DSM-IV and ICD-9 depressive symptoms in the last 14 days. The original version includes10 items and each has five response categories, indicating presence from 'no' (0) to 'all the time' (4). MDI is typically scored either by DSM-IV/ICD-10 algorithm or as a summary index ranging from 0 to 50. Based on a previous validation of the MDI, we chose the summary index over the algorithm scoring method because the index had excellent agreement with depressive disorder (AUC=0.80) (Forsell, 2005). At the cut off of 20 or more points the MDI had high combined sensitivity and specificity for detecting depressive disorders: 0.67 and 0.79 (Forsell, 2005).

Anxiety was at T_0 measured using a revised version of the Sheehan Patient-Rated Anxiety Scale (SPRAS) (Sheehan, 1983; Hällström et al., 2003). Two items, 'sudden unexpected attacks of intense worries or panics' and 'are you afraid that any of these problems will reoccur?', included in DSM-IV, were added, All items in SPRAS refer to amount of distress in the last 30 days with Likert response alternatives ranging from 'not at all' (0) to 'very much' (4), which were dichotomized as present or not, and computed into a summary score (range 0–80). Those with a score of >18 (the 90th percentile) were considered cases.

At T_1, anxiety was measured using the Symptom Checklist (SCL) items for Anxiety (10 items) (Lipman et al., 1979). Questions on 'amount of distress' refer to the last week and were rated on a five-point Likert scale ranging from 'not at all' (0), to 'very much' (4). We computed individual means for the anxiety items. A cut point of 1.75 was used as a diagnostic proxy for any anxiety syndrome (sensitivity and specificity=63.2 and 83.8, AUC=0.80 for detecting any DSM-IV anxiety (Lundin et al., 2015b).

When examining possible reverse associations; depression and anxiety at baseline (T_0) were instead the study exposures.

3.3. Confounders

In this study, we adjusted for potential confounders that have been found to influence the associations between cannabis, depression and anxiety, such as other substance use, education and childhood adverse circumstances (Feingold et al., 2015; Manrique-Garcia et al., 2012; Degenhardt et al., 2012). Furthermore, as previous research indicate that both prevalence of cannabis use and of anxiety and depression may be higher in the Stockholm region as compared to the rest of Sweden (Carlsson et al., 2013; Danielsson and Allebeck, 2015), and that ethnicity may affect the associations examined (Compton et al., 2000), we also accounted for the factors.

One question of *place of upbringing* (before age 18) was used, with tree response categories: Stockholm county, other place in Sweden and abroad. One question of country of birth was used, with two answer alternatives; Sweden and foreign country. Two items on *childhood adverse circumstances* (before age 18) were used; economic deprivation (no, yes, slight and/or for short periods, yes, hard and/or longer periods) and serious family tensions (no, yes, slight and/or for short periods, yes, hard and/or longer periods). *Other illicit drug use* was based on the same item list as where responders indicated if they had ever used cannabis and grouped yes/no. *Education* was obtained from the education register and categorized according to the highest obtained educational level; primary, secondary and tertiary education. *Alcohol consumption* was measured using Audit, which previously has been shown to agree well with risky alcohol use and alcohol use disorder (Lundin et al., 2015a). We used the logged full range of the Audit index as a severity scale.

3.4. Statistical analysis

Log-binomial regressions were used for estimations of relative risks (i.e. risk ratios, RR with 95% confidence intervals, CI) of (1) depression and anxiety at follow-up among baseline cannabis users as compared to non-users and (2) onset of cannabis use at follow-up among those reporting depression/anxiety at baseline compared to non-depression/anxiety.

In our first analysis, we excluded those who at baseline potentially had depression (Major Depression Inventory sum score of >19) (Forsell, 2005), or anxiety (Sheehan Patient Rated Anxiety Scale (SPRAS) score of >18 (Sheehan, 1983; Hällström et al., 2003). For our second analysis, all baseline cannabis users were excluded.

First, possible associations between all the covariates and cannabis and depression/anxiety were tested with Chi square analyses and *T*-tests, and, if significantly associated (95% CI), included in the regression models. Next, crude associations were examined, and thereafter blocks of potential confounders were included step-wise in multivariable models: age, sex, family tensions, other illicit drug use, and Audit. Finally, all potential confounders that affected the estimate were included simultaneously. Because those born abroad had a (non-significant) negative association between cannabis and depression we excluded this group from the analyses. Gender differences were examined by sex-stratified analyses.

In the cohort excluding foreign born ($n=8026$), there were 7027 free from depression and anxiety at baseline that comprised the study base for the cannabis-depression and anxiety analyses. The study base for the cannabis onset among never users was 6724. Regression analyses were carried out on those with full information on baseline variables, and the analytical samples sizes are indicated in their respective table. All estimates were weighted to correct for non-participation, using national records as auxiliary variables. The following auxiliary variables were used to compute the estimated response propensity score (estimated inverse of responding) in a logistic regression model: sex, age (total population register), income (from tax registers, grouped into quartiles), sickness absence (from the tax register), education (from the Education Register), and disability pension (from the National Social Insurance Agency) (Lundin et al., 2015b). All analyses were performed with SAS 9.4.

4. Results

In total, 1275 persons (16.5 percent) out of 8598 reported having ever used cannabis at baseline (Table 1). Mean age at baseline was 34.4 (SD=14.7, range 20–64). Cannabis users, in

Table 1
Distribution of covariate frequencies (%) across cannabis use measured at baseline in a cohort of Swedish men and women.

	Sample		Cannabis *n*	Non-cannabis	Cannabis	Non-cannabis	Chi sq.
	n	weighted	n	*n*	% weighted	% weighted	
Sex							
Male	3616	49.46	661	2955	59.66	47.44	<.0001
Female	4982	50.54	614	4368	40.34	52.34	
Age							
Years (mean with SD)		41.43 (19.1)			34.44 (14.7)	42.05 (18.9)	<.0001
Education							
Primary	1046	15.97	140	906	15.28	16.11	<.0001
Secondary	5535	64.28	862	4673	67.27	64.68	
Tertiary	1991	19.75	269	1722	17.45	16.87	
Childhood circumstances							
Country of birth							
Sweden	8026	89.97	1233	6793	95.43	88.89	
Foreign country	572	10.03	42	530	4.57	11.11	
Place of up-bringing							
Stockholm	4914	57.59	829	4085	66.35	55.82	<.0001
Sweden	3096	35.72	407	2689	30.47	34.36	
Other country	566	8.72	37	529	3.18	9.82	
Economic deprivation							
No	5947	68.35	873	5074	67.76	68.47	0.8295
Yes. slight	2001	23.86	317	1684	25.03	23.63	
Yes. hard	640	7.79	85	555	7.21	7.90	
Tension in family							
No	5514	63.55	670	4844	52.71	65.70	<.0001
Yes. slight	2043	24.27	373	1670	28.95	23.34	
Yes. hard	1029	12.18	231	798	18.34	9.14	
Substance use							
Audit (mean with SD)		4.76 (6.2)			7.35 (8.3)	4.26 (5.5)	<.0001
Other illicit drug use	496	6.95	406	90	65.36	1.47	<.0001
No illicit drug use	8102	93.05	869	7233	34.64	98.53	

Note: Row percentage are weighted, numbers (*n*) are un-weighted. SD=standard deviation.

Table 2
Relative risk of depression and anxiety at three-year follow-up across baseline cannabis use (and across confounders) in a cohort of Swedish men and women.

	Depression ($N=6719$, $n=414$)		Anxiety ($N=6720$, $n=1062$)	
Adjusted for:	RR	95% CI	RR	95% CI
Age and sex	1.22	1.06–1.42	1.38	1.26–1.50
Age, sex and education	1.20	1.03–1.40	1.35	1.24–1.48
Age, sex and place of upbringing	1.21	1.04–1.41	1.37	1.26–1.50
Age, sex and family tension	1.13	0.97–1.32	1.29	1.18–1.41
Age, sex, other illicit drug use	1.08	0.91–1.30	1.25	1.13–1.38
Age, sex, Audit	1.14	0.98–1.33	1.25	1.14–1.37
Age, sex, family tension, other illicit drug use, Audit	0.97	0.82–1.16	1.09	0.99–1.21
All potential confounders	0.99	0.82–1.17	1.09	0.98–1.20
Sex stratified analysis	Depression ($N=3757$, $n=290$)		Anxiety ($N=3757$, $n=674$)	
Women. adjusted for:				
Age	1.28	1.05–1.56	1.28	1.13–1.45
Age, sex and education	1.26	1.04–1.53	1.28	1.13–1.44
Age, sex and place of upbringing	1.27	1.04–1.54	1.28	1.13–1.45
Age, family tension	1.19	0.98–1.46	1.22	1.08–1.38
Age, other illicit drug use	1.20	0.96–1.51	1.18	1.03–1.36
Age, Audit	1.18	0.96–1.44	1.21	1.06–1.37
Age, family tension, other illicit drug use, Audit	1.07	0.85–1.34	1.07	0.93–1.24
All potential confounders	1.09	0.87–1.36	1.08	0.94–1.25
Sex stratified analysis	Depression ($N=2962$, $n=124$)		Anxiety ($N=2963$, $n=388$)	
Men, adjusted for:				
Age	1.10	0.87–1.39	1.47	1.30–1.66
Age, sex and education	1.08	0.86–1.37	1.43	1.27–1.63
Age, sex and place of upbringing	1.08	0.87–1.37	1.46	1.29–1.66
Age, family tension	1.00	0.79–1.26	1.37	1.20–1.55
Age, other illicit drug use	0.90	0.68–1.19	1.31	1.13–1.52
Age, Audit	1.05	0.69–1.19	1.25	1.10–1.42
Age, family tension, other illicit drug use, Audit	0.82	0.62–1.09	1.12	0.97–1.30
All potential confounders	0.82	0.63–1.09	1.11	0.96–1.29

RR from log-binomial. Excluding those $n=$with anxiety or depression at baseline.

comparison to non-users, were to a greater extent male, younger and brought up in Stockholm. Also, cannabis users reported more serious family tension, had a higher alcohol consumption and more alcohol related problems (mean Audit scores=7.35 and 4.26 respectively) and used other illicit drugs to a greater extent; 65.36 percent compared to 1.47 percent among non-cannabis-users.

Adjusted for sex and age, cannabis use at baseline was associated with an increased RR for depression and anxiety at follow-up (Table 2), with RR=1.22 [1.06–1.42 95% Cl] for depression and RR=1.38 [1.26–1.50 95% Cl] for anxiety. When adjusted for family tension, the association between baseline cannabis use and depression three years later was no longer statistically significant. For anxiety, the association was no longer statistically significant when adjustments were made for all confounders simultaneously; in final models; RR=0.99 [0.82–1.17 Cl 95%] for depression and RR=1.09 [0.98–1.20 Cl 95%]. Similar results were found for women and men.

Adjusted for age, reporting depression or anxiety at baseline increased the risk of cannabis onset at follow-up three years later; RR=1.62 [1.28–2.03 95% CI] and RR=1.63 [1.28–2.08 95% CI] respectively (Table 3). When adjusted for confounders, the associations were attenuated substantially and adjusted for other illicit drug use the associations were no longer statistically significant; RR in final models=0.91 [0.72–1.16 95% Cl] for depression and RR=0.93 [0.73–1.18 95% Cl] for anxiety. Similar results were found for women and men, with somewhat stronger associations

Table 3
Relative risk of cannabis onset at three-year follow-up across baseline depression and anxiety (and across confounders) in a cohort of Swedish men and women.

	Cannabis onset Sample ($N=6438$, $n=239$)		Cannabis onset Women ($N=3824$, $n=118$)		Cannabis onset Men ($N=2614$, $n=121$)	
	RR	95%CI	RR	95%CI	RR	95%CI
Depression						
Age	1.62	1.28–2.03	1.42	1.02–1.97	1.87	1.37–2.57
Age, family tension	1.32	1.05–1.67	1.18	0.85–1.64	1.53	1.10–2.12
Age, other illicit drug use	1.24	0.99–1.54	1.15	0.83–1.59	1.34	0.99–1.82
Age, Audit	1.32	1.05–1.66	1.28	0.92–1.78	1.35	0.99–1.85
Age, family tension, other illicit drug use, Audit	0.96	0.76–1.22	0.87	0.62–1.22	0.98	0.70–1.37
All potential confounders	0.91	0.72–1.16	0.82	0.59–1.15	0.95	0.68–1.35
Anxiety	Sample ($N=6443$, $n=240$)		Women ($N=3827$, $n=119$)		Men ($N=2616$, $n=121$)	
Age	1.63	1.28–2.08	1.10	0.75–1.62	2.23	1.66–3.00
Age, family tension	1.33	1.04–1.70	0.91	0.61–1.35	1.86	1.36–2.52
Age, other illicit drug use	1.20	0.96–1.50	0.78	0.53–1.15	1.46	1.08–1.99
Age, Audit	1.41	1.11–1.79	1.06	0.72–1.57	1.65	1.23–2.22
Age, family tension. other illicit drug use, Audit	1.00	0.78–1.27	0.78	0.53–1.14	1.14	0.82–1.59
All potential confounders	0.93	0.73–1.18	0.75	0.51–1.10	1.11	0.80–1.55

Note: RR from log-binomial. Excluding those $n=1275$ using cannabis at baseline.

between baseline depression and anxiety and cannabis onset at follow-up among the males.

5. Discussion

Our results suggest that cannabis use is neither associated with depression nor with anxiety three years later. Also, reporting depression or anxiety at baseline did not increase the risk of cannabis onset at three-year follow-up.

In general, previous studies have reported mixed evidence regarding these associations; this due to differences between studies in definitions of cannabis use and of depression and anxiety and, particularly, in number and type of confounders included (Lev-Ran et al., 2014). In a study by Feingold et al. (2015) major depressive disorder was found to be associated with incidence of cannabis use and this has also been noted in clinical observations (Crippa et al., 2009). A study by Temple et al. (2014) showed that pre-existing anxiety was associated with higher average levels of cannabis intoxication, which in turn was linked to acute anxiety responses due to cannabis use.

One recent meta-analysis, pooling 15 studies, concluded that anxiety is positively related to cannabis use, even if the associations were rather small in magnitude (OR=1.24) (Kedzior and Laeber, 2014). Also, the extent to which the included studies had adjusted for potential confounders varied largely; several had only controlled for demographics and/or other substance use, which raises the question of possible residual confounding.

A recent British study showed an association between cannabis use and later depression, but not with later anxiety (Gage et al., 2015) and yet another study, pooling data from four cohorts in Australia and New Zealand, found that frequent cannabis use was associated with a slightly increased risk of depression (Horwood et al., 2012). In this latter study, however, they presented inconclusive results regarding the direction of causality.

One possible explanation to our somewhat divergent results is the cannabis measure used. Hayatbakhsh et al. (2007) found that frequent cannabis users at age 21 were more likely to report anxiety and depression. Also, among the frequent users, adolescents with an early onset reported even higher risks for later mood disorders (Hayatbakhsh et al., 2007). Another possible explanation is our choice of confounders. In line with previous studies (e.g. Manrique-Garcia et al., 2012), our results highlight the importance of childhood adverse circumstances, such as family tension, in the association between cannabis use and mood disorders. However, what is also clear from our results is the importance of other illicit drug use. One might argue that cannabis use precede other illicit drug use and prior studies have in fact shown that frequent cannabis use increases the risk of other illicit drug use uptake (e.g. Swift et al., 2011). Unfortunately, we have no knowledge of the timing of drug use initiation.

Thus, there are some methodical considerations to this study. We lack information on age of initiation of cannabis use and on frequency of use. It was therefore not possible to assess if longer and heavier use are more strongly associated with depression and anxiety. Furthermore, our sample comprises adults; age 20–64 years, and this may also explain the differences in results. Many previous studies have focused on adolescents, had a cross-sectional design or a follow-up period covering adolescence/late adolescence only (Kedzior and Laeber, 2014; Lev-Ran et al., 2014). Moreover, cannabis use in Stockholm and Sweden is not as prevalent as in other countries, e.g. the Netherlands or the UK, and the sample might be too small for the relatively small associations to reach significance. It might be added though, that cannabis use levels in Sweden have remained unchanged in the last decade (Emcdda, 2015) Anxiety was, unlike depression, measured with different scales at baseline and follow up which might have led to differential associations. We are not aware of any study which has studied the agreement between the two scales, but both the SPRAS and the SCL anxiety scale contain similar items on panic attacks and irrational unexpected fears.

In our study, the population characteristics of the interview participants were, after weighting, similar to the framed population (Lundin et al., 2015a), but it might still be that there is a selection bias. Other health surveys have shown that non-respondents have an increased risk of alcohol-, drug- and smoking-related mortality and morbidity compared with respondents (Christensen et al., 2015), which indicate more unfavorable health among non-respondents and thus an underestimation of actual subjects.

Our study showed that cannabis users had higher alcohol consumption and used other illicit drugs to a much greater extent than non-cannabis-users. Previous studies have reported on a strong relationship between substance use, anxiety and mood disorders (Vorspan et al., 2015; Pacek et al., 2013; Xiong-Lai et al., 2015), comorbidities that evidently are of clinical importance.

Declaration of interest

None

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